

L4 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:214923 CAPLUS
DOCUMENT NUMBER: 136:246402
TITLE: Isolated nucleic acid molecules which encode T cell inducible factors (TIFs), the proteins encoded, and uses thereof in prepn. of antibodies and immunogens and in study of STAT activation and interleukin-9 effects

INVENTOR(S): Dumoutier, Laure; Louhed, Jamila;
Renauld, Jean-Christophe
PATENT ASSIGNEE(S): Ludwig Institute for Cancer Research, USA
SOURCE: U.S., 23 pp., Cont.-in-part of U.S. Ser. No. 178,973.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6359117	B1	20020319	US 1999-354243	19990716
US 6274710	B1	20010814	US 1998-178973	19981026
WO 2000024758	A1	20000504	WO 1999-US24424	19991018
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9965206	A1	20000515	AU 1999-65206	19991018
BR 9914777	A	20010703	BR 1999-14777	19991018
EP 1131333	A1	20010912	EP 1999-953231	19991018
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6331613	B1	20011218	US 1999-419568	19991018
US 2001024652	A1	20010927	US 2000-751797	20001229
PRIORITY APPLN. INFO.: US 1998-178973 A2 19981026 US 1999-354243 A 19990716 US 1999-419568 A1 19991018 WO 1999-US24424 W 19991018				

AB The invention involves isolation of nucleic acid mols., the expression of which is upregulated by interleukin-9. The amino acid sequences of the proteins which correspond to the nucleic acid mols. show some structural features of cytokines. The mols. are referred to as T cell inducible factors (TIFs). In addn. to the nucleic acid mols. and the proteins, various uses of the mols. are disclosed. One of the examples describes the use of the mols. in manuf. of antibodies which bind to the TIF protein. Such antibodies, monoclonal or polyclonal, constitute a further feature of the invention as do fragments of said antibodies, chimeric forms, humanized forms, and recombinant forms.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 7 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002183350 EMBASE
TITLE: Viral and cellular interleukin-10 (IL-10)-related cytokines: From structures to functions.
AUTHOR: Dumoutier L.; Renauld J.-C.
CORPORATE SOURCE: J.-C. Renauld, Ludwig Inst. for Cancer Research, UCL 74 59, Avenue Hippocrate, 74, B-1200 Brussels, Belgium.
jean-christophe.renauld@bru.licr.org
SOURCE: European Cytokine Network, (2002) 13/1 (5-15).
Refs: 97
ISSN: 1148-5493 CODEN: EYNEJ
COUNTRY: France
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The anti-inflammatory and immunosuppressive activities of IL-10 have been extensively studied during the last 10 years. More recently a series of new cytokines, structurally related to IL-10, were described. This family includes mda-7, IL-19, IL-20, IL-TIF/IL-22, and AK155. Most of the biological functions of these cytokines remain to be unraveled but new data are coming out steadily. Although none of these "IL-10 homologs" mimics IL-10 activities, they are likely to be involved in inflammatory processes as well. mda-7, IL-19 and IL-20 form a subfamily within IL-10 homologs, based on conserved amino acid sequences, and on the use of shared receptor complexes. Functional studies have stressed the potential suppressing activity of mda-7 on tumor growth. As for IL-20, its overexpression in transgenic mice led to skin abnormalities, reminiscent of psoriatic lesions in humans. IL-TIF/IL-22 is a Th1 cytokine, and was shown to upregulate the acute phase reactant production by liver cells. Finally, for AK155, originally described as a gene induced upon T cell transformation by Herpes-virus saimiri, functional data are still lacking to determine its biological activities.

L4 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:916420 CAPLUS
DOCUMENT NUMBER: 136:52731
TITLE: Isolated nucleic acid molecules which encode T cell inducible factors (TIFs), the proteins encoded, and uses thereof
INVENTOR(S): Dumoutier, Laure; Louhed, Jamila;
Renauld, Jean-Christophe
PATENT ASSIGNEE(S): Ludwig Institute for Cancer Research, USA
SOURCE: U.S., 24 pp., Cont.-in-part of U.S. Ser. No. 354,243.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6331613	B1	20011218	US 1999-419568	19991018
US 6274710	B1	20010814	US 1998-178973	19981026
US 6359117	B1	20020319	US 1999-354243	19990716
US 2001024652	A1	20010927	US 2000-751797	20001229
PRIORITY APPLN. INFO.: US 1998-178973 A2 19981026 US 1999-354243 A2 19990716 US 1999-419568 A1 19991018				

AB The invention involves isolation of nucleic acid mols., the expression of which are upregulated by interleukin-9. The amino acid sequences of the proteins which correspond to the nucleic acid mols. show some structural features of cytokines. In addn. to the nucleic acid mols. and the proteins, various uses of the mols. are disclosed. The mols. are referred to as T cell inducible factors.

L4 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:291060 CAPLUS
DOCUMENT NUMBER: 132:333389
TITLE: Isolated nucleic acid molecules which encode T cell inducible factors (TIFs), the proteins encoded, and uses thereof
INVENTOR(S): Dumoutier, Laure; Louhed, Jamila; Renault, Jean-christophe
PATENT ASSIGNEE(S): Ludwig Institute for Cancer Research, USA
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000024758	A1	20000504	WO 1999-US24424	19991018
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6274710	B1	20010814	US 1998-178973	19981026
US 6359117	B1	20020319	US 1999-354243	19990716
AU 9965206	A1	20000515	AU 1999-65206	19991018
BR 9914777	A	20010703	BR 1999-14777	19991018
EP 1131333	A1	20010912	EP 1999-953231	19991018
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.:
US 1998-178973 A 19981026
US 1999-354243 A 19990716
WO 1999-US24424 W 19991018
AB The invention involves isolation of nucleic acid mols. encoding TIFs, the expression of the TIFs which are upregulated by interleukin-9. The amino acid sequences of the TIF proteins which correspond to the nucleic acid mols. show some structural features of cytokines. In addn. to the nucleic acid mols. and the TIF proteins, use of the mols. for detg. effectiveness of interleukin 9, for stimulating STAT protein, for inhibiting activation of STAT protein are disclosed. Also provided are TIF inhibitor comprising antibodies and antisense mols. TIF mutein is useful for alleviating asthma or allergy.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2002 ACS

DUPLICATE 1

ACCESSION NUMBER: 2000:633242 CAPLUS
DOCUMENT NUMBER: 133:320857
TITLE: Human interleukin-10-related T cell-derived inducible factor: molecular cloning and functional characterization as an hepatocyte-stimulating factor
AUTHOR(S): Dumoutier, Laure; Van Roost, Emiel; Colau, Didier; Renault, Jean-Christophe
CORPORATE SOURCE: Ludwig Institute for Cancer Research, Brussels Branch and the Experimental Medicine Unit, Christian de Duve Institute of Cellular Pathology, Universite Catholique de Louvain, Brussels, B1200, Belg.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2000), 97(18), 10144-10149
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB IL-10-related T cell-derived inducible factor (IL-TIF or IL-21) is a new cytokine structurally related to IL-10 and originally identified in the mouse as a gene induced by IL-9 in T cells and mast cells. Here, the authors report the cloning of the human IL-TIF cDNA, which shares 79% amino acid identity with mouse IL-TIF and 25% identity with human IL-10. Recombinant human IL-TIF was found to activate signal transducer and activator of transcription factors-1 and -3 in several hepatoma cell lines. IL-TIF stimulation of HepG2 human hepatoma cells up-regulated the prodn. of acute phase reactants such as serum amyloid A, alpha-1-antichymotrypsin, and haptoglobin. Although IL-10 and IL-TIF have distinct activities, antibodies directed against the .beta. chain of the IL-10 receptor blocked the induction of acute phase reactants by IL-TIF, indicating that this chain is a common component of the IL-10 and IL-TIF receptors. Similar acute phase reactant induction was obsd. in mouse liver upon IL-TIF injection, and IL-TIF expression was rapidly increased after lipopolysaccharide (LPS) injection, suggesting that this cytokine contributes to the inflammatory response in vivo.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 7

MEDLINE

DUPLICATE 2

ACCESSION NUMBER: 2000126044 MEDLINE
DOCUMENT NUMBER: 20126044 PubMed ID: 10657629
TITLE: Cloning and characterization of IL-10-related T cell-derived inducible factor (IL-TIF), a novel cytokine structurally related to IL-10 and inducible by IL-9.
AUTHOR: Dumoutier L; Louhed J; Renault J
CORPORATE SOURCE: Ludwig Institute for Cancer Research, Brussels, Belgium.
SOURCE: JOURNAL OF IMMUNOLOGY, (2000 Feb 15) 164 (4) 1814-9.
JOURNAL code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
OTHER SOURCE: GENBANK-AJ249491; GENBANK-AJ249492
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000320
Last Updated on STN: 20000320
Entered Medline: 20000309
AB IL-9 is a Th2 cytokine active on various cell types such as T and B lymphocytes, mast cells, and eosinophils, and potentially involved in

allergy and asthma. To understand better the molecular mechanisms underlying the activity of this cytokine, we used a cDNA subtraction method to identify genes specifically induced by IL-9 in mouse T cells. One of the IL-9-regulated genes isolated by this approach turned out to encode a 180-amino acid long protein, including a potential signal peptide, and showing 22% amino acid identity with IL-10. This protein, designated IL-10-related T cell-derived inducible factor (IL-TIF), is induced by IL-9 in thymic lymphomas, T cells, and mast cells, and by lectins in freshly isolated splenocytes. Experiments concerning the mechanism regulating IL-TIF expression in T cells indicate that IL-9 induction is rapid (within 1 h), does not require protein synthesis, and depends on the activation of the Janus kinase (JAK)-STAT pathway. In vivo, constitutive expression of IL-TIF was detected by RT-PCR in thymus and brain, suggesting that the role of this new factor is not restricted to the immune system. Transfection of HEK293 cells with the IL-TIF cDNA resulted in the production of a glycosylated protein of about 25 kDa that was found to induce STAT activation in mesangial and neuronal cell lines. Further studies will have to address the possibility that some of the IL-9 activities may be mediated by IL-TIF.

L4 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
 ACCESSION NUMBER: 2000:468282 BIOSIS
 DOCUMENT NUMBER: PREV200000468282
 TITLE: IL-TIF induces acute phase reactant production by hepatocytes through IL-10Rbeta.
 AUTHOR(S): Dumoutier, L. (1); Van Roost, E. (1); Colau, D. (1); Renauld, J.-C. (1)
 CORPORATE SOURCE: (1) Brussels Branch, Ludwig Institute for Cancer Research, Brussels Belgium
 SOURCE: Immunology Letters, (September, 2000) Vol. 73, No. 2-3, pp. 261. print.
 Meeting Info.: 24th European Immunology Meeting of the European Federation of Immunological Societies (EFIS) Poznan, Poland September 23-26, 2000 European Federation of Immunological Societies
 . ISSN: 0165-2478.
 DOCUMENT TYPE: Conference
 LANGUAGE: English
 SUMMARY LANGUAGE: English

=> dis his

(FILE 'HOME' ENTERED AT 18:03:53 ON 24 JUN 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 18:04:22 ON 24 JUN 2002

L1 431 S DUMOUTIER L?/AU OR LOUAHED J?/AU OR RENAULD J?/AU
 L2 71 S L1 AND STAT?
 L3 11 S L2 AND TIF
 L4 7 DUP REM L3 (4 DUPLICATES REMOVED)

=> s (stat (1N) 3) (P) TIF?
 L5 1 (STAT (1N) 3) (P) TIF?

=> s (stat (1N) 3) and TIF?
 L6 2 (STAT (1N) 3) AND TIF?

=> dis 16 1-2 ibib abs

L6 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
 ACCESSION NUMBER: 2001:264637 BIOSIS
 DOCUMENT NUMBER: PREV200100264637
 TITLE: Human IL-22 (IL-TIF) is a novel homolog of IL-10 that phosphorylates STAT 3 in colon carcinoma cells expressing the IL-22R1 chain.
 AUTHOR(S): Nagalakshmi, Marehalli L. (1); Parham, Christi (1); Rasclé, Ann (1); Menon, Satish (1); Moore, Kevin (1); de Weal Malefyt, Rene (1)
 CORPORATE SOURCE: (1) DNAX Research Institute, 901 California Ave, Palo Alto, CA, 94304 USA
 SOURCE: FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1052. print.
 Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
 ISSN: 0892-6638.
 DOCUMENT TYPE: Conference
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB DNA database mining and bioinformatics have revealed the existence of several novel proteins that have 'IL-10 like' structural motifs. Human IL-22 is one such protein has been described as a hepatocyte stimulatory factor inducing the production of acute phase proteins from hepatocytes. IL-22 binds to its specific receptor comprising the IL-22 R1 and the IL-10R2 (CRF2-4) chains. This interaction leads to the activation of signal transducer and activator of transcription factors (STATs-1 and -3). Quantitative PCR analysis (TagMan) showed that human IL-22 mRNA is expressed in activated T cell cDNA libraries. The IL-22R1 chain mRNA is highly upregulated in normal and diseased colon cell libraries. Expression of this receptor chain was at very low levels in resting and activated monocyte, T, B and dendritic cell cDNA libraries. The second receptor component, the IL-10R2 chain is known to be expressed ubiquitously. In addition, we have shown that human IL-22 obtained from transient transfections activates STAT-3 in a colon carcinoma cell line, Colo205. Unstimulated cells expressed levels of IL-22R1 chain mRNA comparable to the human hepatoma cell line, HepG2. Levels of mRNA of the acute phase proteins - serum amyloid A, alpha - Antichymotrypsin and Haptoglobin were upregulated in IL-22 treated Colo205 cells. Future studies will be directed to identify the biological activities of this protein.

L6 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
 ACCESSION NUMBER: 2000:440537 BIOSIS
 DOCUMENT NUMBER: PREV200000440537
 TITLE: Human interleukin-10-related T cell-derived inducible factor: Molecular cloning and functional characterization as an hepatocyte-stimulating factor.
 AUTHOR(S): Dumoutier, Laure; Van Roost, Emiel; Colau, Didier; Renauld, Jean-Christophe (1)
 CORPORATE SOURCE: (1) Brussels Branch and Experimental Medicine Unit, Ludwig Institute for Cancer Research, Christian de Duve Institute of Cellular Pathology, Universite Catholique de Louvain,

SOURCE: Avenue Hippocrate 74, B1200, Brussels Belgium
Proceedings of the National Academy of Sciences of the
United States of America, (August 29, 2000) Vol. 97, No.
18, pp. 10144-10149. print.
ISSN: 0027-8424.

DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB IL-10-related T cell-derived inducible factor (IL-TIF or IL-21)
is a new cytokine structurally related to IL-10 and originally identified
in the mouse as a gene induced by IL-9 in T cells and mast cells. Here, we
report the cloning of the human IL-TIF cDNA, which shares 79%
amino acid identity with mouse IL-TIF and 25% identity with
human IL-10. Recombinant human IL-TIF was found to activate
signal transducer and activator of transcription factors-1 and -3 in
several hepatoma cell lines. IL-TIF stimulation of HepG2 human
hepatoma cells up-regulated the production of acute phase reactants such
as serum amyloid A, alpha₁-antichymotrypsin, and haptoglobin. Although
IL-10 and IL-TIF have distinct activities, antibodies directed
against the beta chain of the IL-10 receptor blocked the induction of
acute phase reactants by IL-TIF, indicating that this chain is a
common component of the IL-10 and IL-TIF receptors. Similar
acute phase reactant induction was observed in mouse liver upon IL-
TIF injection, and IL-TIF expression was found to be
rapidly increased after lipopolysaccharide (LPS) injection, suggesting
that this cytokine contributes to the inflammatory response in vivo.

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=> s (stat (1N) 3) (P) ((IL (1N) 21) or (IL (1N) 22))
L7 6 (STAT (1N) 3) (P) ((IL (1N) 21) OR (IL (1N) 22))

=> dup rem l7

PROCESSING COMPLETED FOR L7

L8 3 DUP REM L7 (3 DUPLICATES REMOVED)

=> dis l8 1-3 ibib abs

L8 ANSWER 1 OF 3 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:264637 BIOSIS

DOCUMENT NUMBER: PREV200100264637

TITLE: Human IL-22 (IL-TIF) is a
novel homolog of IL-10 that phosphorylates STAT
3 in colon carcinoma cells expressing the IL-22R1
chain.

AUTHOR(S): Nagalakshmi, Marehalli L. (1); Parham, Christi (1); Rascle,
Ann (1); Menon, Satish (1); Moore, Kevin (1); de Weal
Malefyt, Rene (1)

CORPORATE SOURCE: (1) DNAX Research Institute, 901 California Ave, Palo Alto,
CA, 94304 USA

SOURCE: FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1052.
print.
Meeting Info.: Annual Meeting of the Federation of American
Societies for Experimental Biology on Experimental Biology
2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.

DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB DNA database mining and bioinformatics have revealed the existence of
several novel proteins that have 'IL-10 like' structural motifs. Human
IL-22 is one such protein has been described as a
hepatocyte stimulatory factor inducing the production of acute phase
proteins from hepatocytes. IL-22 binds to its specific
receptor comprising the IL-22 R1 and the IL-10R2
(CRF2-4) chains. This interaction leads to the activation of signal
transducer and activator of transcription factors (STATs-1 and -3).
Quantitative PCR analysis (TaqMan) showed that human IL-
22 mRNA is expressed in activated T cell cDNA libraries. The
IL-22R1 chain mRNA is highly upregulated in normal and diseased colon cell
libraries. Expression of this receptor chain was at very low levels in
resting and activated monocyte, T, B and dendritic cell cDNA libraries.
The second receptor component, the IL-10R2 chain is known to be expressed
ubiquitously. In addition, we have shown that human IL-
22 obtained from transient transfections activates STAT-
3 in a colon carcinoma cell line, Colo205. Unstimulated cells
expressed levels of IL-22R1 chain mRNA comparable to the human hepatoma
cell line, HepG2. Levels of mRNA of the acute phase proteins - serum
amyloid A, alpha₁ - Antichymotrypsin and Haptoglobin were upregulated in
IL-22 treated Colo205 cells. Future studies will be
directed to identify the biological activities of this protein.

L8 ANSWER 2 OF 3 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2002:261534 BIOSIS

DOCUMENT NUMBER: PREV200200261534

TITLE: The interleukin-2 (IL-2) receptor common gamma chain
(gammac) is a required signaling component of the IL-21
receptor and supports IL-21-induced cell proliferation via
JAK3.

AUTHOR(S): Habib, Tania J. (1); Weinberg, Kenneth I.; Kaushansky,
Kenneth (1)

CORPORATE SOURCE: (1) University of Washington, Seattle, WA USA

SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp.
818a. <http://www.bloodjournal.org/>. print.
Meeting Info.: 43rd Annual Meeting of the American Society
of Hematology, Part 1 Orlando, Florida, USA December 07-11,
2001
ISSN: 0006-4971.

DOCUMENT TYPE: Conference
LANGUAGE: English

AB The newly described lymphokines human and murine interleukin-21
(IL-21) are 131 and 122 amino acid polypeptides
produced by activated CD4⁺ lymphocytes. Structurally, IL-
21 is most closely related to IL-2 and IL-15, and although
IL-21 alone cannot support the proliferation of any
subclass of lymphocytes, it profoundly affects the growth and activation
state of B-, T and NK cells in concert with other lymphokines or stimuli.
The biological effects of IL-21 are mediated through a
538 amino acid class I member of the hematopoietic cytokine receptor
superfamily (IL-21Ralpha). Although the complete IL-21R has not yet been
defined, IL-21Ralpha is structurally similar to the beta subunit of the
receptor for IL-2 and IL-15 (IL-2/15Rbeta) and thus, might utilize the

gammac chain for signaling. To test this hypothesis we used the gammac-deficient X-linked severe combined immunodeficiency B cell line JT, and JT cells reconstituted with gammac (JT-gammac). Moreover, we examined the functional requirement of both gammac and the gammac-associated Janus family tyrosine kinase 3 (JAK3) in IL-21-induced proliferation of pro-B-lymphoid cells engineered to express human IL-21Ralpha (BaF3/IL-21Ralpha). Using immunoprecipitation and Western blotting we found that IL-21 stimulated prominent tyrosine phosphorylation (Tyr-P) of JAK1 and JAK3 in BaF3/IL-21Ralpha, primary murine splenic B cells, and JT-gammac. In contrast, IL-21 failed to induce Tyr-P of JAK1 and JAK3 in JT cells. Moreover, STATs 1, 3 and 5 underwent Tyr-P in response to IL-21 in BaF3/IL-21Ralpha-, primary B- and JT-gammac cells but not in JT cells. To determine the functional role of gammac in IL-21 signaling, we conducted MTT proliferation assays with JT-gammac cells and found a specific proliferative response to IL-21; JT cells failed to respond to IL-21. Neutralizing monoclonal antibodies specific for the gammac chain effectively inhibited IL-21-induced growth of BaF3/IL-21Ralpha cells in an MTT assay, further supporting a functional role for this molecule in IL-21R signaling. Finally, the potent and specific JAK3 tyrosine kinase inhibitor WHI-P131 significantly reduced IL-21-induced proliferation of BaF3/IL-21Ralpha cells relative to the vehicle control. Taken together, these results definitively demonstrate that IL-21-mediated signaling requires the gammac chain of the IL-2 receptor, and indicate that JAK3 is an essential transducer of gammac-dependent survival and/or mitogenic signals induced by this cytokine.

L8 ANSWER 3 OF 3 MEDLINE DUPLICATE 1
 ACCESSION NUMBER: 2001023984 MEDLINE
 DOCUMENT NUMBER: 20469498 PubMed ID: 10875937
 TITLE: Interleukin (IL)-22, a novel human cytokine that signals through the interferon receptor-related proteins CRF2-4 and IL-22R.
 AUTHOR: Xie M H; Aggarwal S; Ho W H; Foster J; Zhang Z; Stinson J; Wood W I; Goddard A D; Gurney A L
 CORPORATE SOURCE: Department of Molecular Biology, Genentech, Inc., South San Francisco, California 94080, USA.
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Oct 6) 275 (40) 31335-9.
 PUB. COUNTRY: Journal code: 2985121R. ISSN: 0021-9258.
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 OTHER SOURCE: GENBANK-AF279437; GENBANK-AF286095
 ENTRY MONTH: 200011
 ENTRY DATE: Entered STN: 20010322
 Last Updated on STN: 20010322
 Entered Medline: 20001113

AB We report the identification of a novel human cytokine, distantly related to interleukin (IL)-10, which we term IL-22. IL-22 is produced by activated T cells. IL-22 is a ligand for CRF2-4, a member of the class II cytokine receptor family. No high affinity ligand has yet been reported for this receptor, although it has been reported to serve as a second component in IL-10 signaling. A new member of the interferon receptor family, which we term IL-22R, functions as a second component together with CRF2-4 to enable IL-22 signaling. IL-22 does not bind the IL-10R. Cell lines were identified that respond to IL-22 by activation of STATs 1, 3, and 5, but were unresponsive to IL-10. In contrast to IL-10, IL-22 does not inhibit the production of proinflammatory cytokines by monocytes in response to LPS nor does it impact IL-10 function on monocytes, but it has modest inhibitory effects on IL-4 production from Th2 T cells.

=> dis his

(FILE 'HOME' ENTERED AT 18:03:53 ON 24 JUN 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 18:04:22 ON 24 JUN 2002

L1 431 S DUMOUTIER L?/AU OR LOUAHED J?/AU OR RENAULD J?/AU
 L2 71 S L1 AND STAT?
 L3 11 S L2 AND TIP
 L4 7 DUP REM L3 (4 DUPLICATES REMOVED)
 L5 1 S (STAT (1N) 3) (P) TIP?
 L6 2 S (STAT (1N) 3) AND TIP?
 L7 6 S (STAT (1N) 3) (P) ((IL (1N) 21) OR (IL (1N) 22))
 L8 3 DUP REM L7 (3 DUPLICATES REMOVED)

=> end

ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF

LOGOFF? (Y)/N/HOLD:y

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
59.32	59.53

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
-2.48	-2.48

CA SUBSCRIBER PRICE

STN INTERNATIONAL LOGOFF AT 18:13:42 ON 24 JUN 2002

WEST Search History

DATE: Monday, June 24, 2002

Set Name Query
side by side

Hit Count Set Name
result set

DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR

L15	(stat adj 3) and (IL adj 10)	3	L15
L14	(stat adj 3) and ((IL adj 21) or (IL adj 22))	2	L14
L13	(stat adj 3) same ((IL adj 21) or (IL adj 22))	0	L13
L12	(stat? or (IL adj 21) or (IL adj 22))	2108917	L12
L11	L10 and (stat? or (IL adj 21) or (IL adj 22))	7	L11
L10	(dumoutier)[IN] OR (louahed)[IN] or (renauld) [in]	154	L10
L9	(dumoutier)[IN] OR (louahed)[IN]	20	L9
L8	(ulex adj europaeus adj II) or UEAI	11	L8
L7	L6 and mbl	2	L7
L6	(stahl)[IN] OR (lekowski)[IN]	3181	L6
L5	(murine or mouse) same (inhibit\$4) same (myoblast\$4) same (different\$4)	2	L5
L4	striamin	1	L4
L3	L2 and striamin	1	L3
L2	(wadhwa)[IN] OR (kaul)[IN] or (reddel)[in]	839	L2
L1	(wadhwa)[IN] OR (kaul)[IN]	816	L1

END OF SEARCH HISTORY

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 18:04:22 ON 24 JUN 2002

L1 431 S DUMOUTIER L?/AU OR LOUAHED J?/AU OR RENAULD J?/AU
L2 71 S L1 AND STAT?
L3 11 S L2 AND TIF
L4 7 DUP REM L3 (4 DUPLICATES REMOVED)
L5 1 S (STAT (1N) 3) (P) TIF?
L6 2 S (STAT (1N) 3) AND TIF?
L7 6 S (STAT (1N) 3) (P) ((IL (1N) 21) OR (IL (1N) 22))
L8 3 DUP REM L7 (3 DUPLICATES REMOVED)